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Environmental tobacco smoke and the risk of cardiovascular disease

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Disease risk due to smoking is not limited to smokers only. Passive smoking, exposure to environmental tobacco smoke, is associated with adverse health effects, and it increases the risk of several diseases. This paper summarizes the cardiovascular effects of tobacco smoke and the current data on the effects of environmental tobacco smoke on the development of cardiovascular disease. According to the results of epidemiologic and experimental studies, environmental tobacco smoke has marked harmful effects on the cardiovascular system. It is estimated that it increases the risk of an acute event of coronary heart disease by 25–35%. Even though the number of studies conducted in the work environment is small, there is no reason to assume that the cardiovascular effects of environmental tobacco smoke differ markedly between the home and the workplace. Firm and timely actions are needed to protect people from exposure to environmental tobacco smoke, both in occupational and other environments.

Key terms coronary heart disease, disease, epidemiology, experimental studies, overview, passive smoking, smoking, stroke, subclinical effect, tobacco.

Smoking affects virtually every organ system (1). Disease risk due to smoking is not limited to smokers only. Passive smoking, exposure to environmental tobacco smoke, is linked with adverse health effects and increases the risk of several diseases, such as lung cancer, other respiratory diseases, and low birthweight (2). There is increasing evidence that exposure to environmental tobacco smoke also increases the risk of cardiovascular disease (CVD).

Tobacco smoke contains over 4000 chemicals, from which at least 40 are carcinogens (1). The cardiovascular effects of these chemicals are not so well known even though, according to epidemiologic data, from the public health point of view CVD is the most important disease caused by smoking (3)

Environmental tobacco smoke originates from the smoldering of a cigarette or other tobacco product. The smoke dilutes in the ambient air, diffuses, and spreads through it. The composition of the smoke inhaled by a smoker, generally referred to as mainstream smoke, differs from the smoke inhaled by others, generally referred to as sidestream smoke (4). Sidestream smoke may be even more harmful to health than mainstream smoke (5, 6).

In our overview we summarize the cardiovascular effects of tobacco smoke and current data from the most relevant epidemiologic and experimental studies on the effects of environmental tobacco smoke on the development of CVD.

Risk of cardiovascular disease among active smokers

Smoking was recognized as a risk factor for CVD already in the 1950s (7). Since then numerous studies have confirmed the association (8–14). Most studies report a 1.5 to 2.5 times greater risk of coronary heart disease (CHD) and stroke for smokers than for nonsmokers. The relative risk tends to be larger in case-referent studies than in prospective cohort studies.

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When a person quits smoking, the risk of CVD decreases rapidly (13, 15–18). The risk of myocardial infarction of a former smoker after a smoke-free period of 5 years is only 0–30% higher than the risk of a nonsmoker. The decrease in CHD risk is fairly independent of the amount of smoking prior to the person's quitting (3). On the other hand, even relatively light smoking, from one to five cigarettes a day, increases the risk of CHD significantly (19). Occasional smoking has been shown to increase CVD risk (20). Thus a relatively small and infrequent exposure to mainstream tobacco smoke increases the risk of CVD, but the effect of tobacco smoke on the disease risk seems to be largely reversible.

Cerebral and peripheral circulation is also affected by smoking. The relative risk of stroke due to smoking has been reported to be similar to the risk of CHD, or even higher (21–24). Damage to peripheral circulation causes intermittent claudication and, later, limb amputation. Smoking combined with diabetes causes a particular risk for damage to peripheral circulation (25). Other circulatory events, such as the formation and rupture of aneurysms in abdominal aorta, are also more common in smokers than in nonsmokers (26, 27).

Cardiovascular effects of tobacco smoke

At least the following five mechanisms have been proposed by which tobacco smoke contributes to the clinical manifestations of CVD: atherosclerosis, thrombosis, coronary artery spasms, cardiac arrhythmia, and reduced capacity of blood to deliver oxygen (28–30). Depending on the mechanism, the effects of tobacco smoke on CVD risk are both acute and cumulative.

The most important acute effects of tobacco smoke may be its arrhythmic effect and its effect on the hemostatic system and thrombotic process (31–34). The arrhythmic effect appears particularly among subjects with an already compromised coronary circulation by increasing myocardial irritability and triggering sudden death (31, 32). Smoking increases the levels of serum fibrinogen and affects also other components of the hemostatic system (33, 34). Hemostatic effects of tobacco smoke appear soon after the start of exposure, and the effects diminish gradually after exposure has stopped (35). Data from epidemiologic studies support the acute or subacute nature of the cardiovascular effects of tobacco smoke. It has been suggested that a substantial part of the increase in CHD risk caused by smoking is mediated through the increase in fibrinogen concentration (35, 36). The effect of passive smoking on fibrinogen concentration has been estimated to be about 40–60% of the effect of active smoking (37).

Smoking is also directly involved in the formation of atherosclerotic lesions in the arterial wall (38). In addition, smoking is associated with a more atherogenic lipid profile, as reflected by decreased levels of high-density lipoprotein (HDL) cholesterol and an increased total-to-HDL cholesterol ratio in serum (39). Atherosclerotic changes are only partly reversible (40).

There are fairly few data available on which of the numerous substances in tobacco smoke are involved in the development of CVD. The effects of tobacco smoke on the cardiovascular system are probably caused by many elements, including carbon monoxide, nicotine, and polycyclic aromatic hydrocarbons, as well as other, not fully specified components of smoke (41). Recent genetic studies have suggested that the chemicals in cigarette smoke that are substrates for glutathione S-transferases may be involved in the etiology of CHD (42).

The role of nicotine in CVD risk is arguable. Hemodynamic changes caused by nicotine, such as a temporary increase in blood pressure and heart rate, may promote the rupture of atherosclerotic plaques, the formation of blood clots, and arterial thrombosis (30). Hemodynamic changes are mediated through a nicotine-induced release of noradrenaline in a dose-dependent manner (43). Nicotine is, however, probably not responsible for all the harmful effects of smoking. When the metabolic and hemostatic effects were compared between active smokers and ex-smokers using nicotine replacement therapy, active smokers had lower HDL cholesterol levels and fibrinolytic activity, but there was no difference in the blood noradrenaline or serotonin concentrations (44).

Epidemiologic evidence of a relationship between environmental tobacco smoke and risk of cardiovascular disease

The CVD risk associated with environmental tobacco smoke can be studied either by direct or indirect methods. In direct analyses the risk of nonsmokers is compared with the risk of unexposed nonsmokers. Most of the studies have been conducted in occupational environments or domestic settings with spousal smoking. With the indirect method, the risk of exposed persons is estimated from the risk of active smokers.

In case-referent and prospective cohort studies, the end point is usually an acute CVD event, such as fatal or nonfatal myocardial infarction or stroke. The association of environmental tobacco smoke with subclinical vascular damage, such as carotid artery intima-media thickness (IMT), brachial artery endothelial dysfunction, silent cerebral infarctions, and changes in the hemostatic system, can also be studied.

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Risk of an acute event of coronary heart disease in association with exposure to environmental tobacco smoke

In recent years, several meta-analyses and reviews have been published on the risk of CVD in association with exposure to environmental tobacco smoke (45–51) (table 1). Most of the studies included in these meta-analyses and studies on stroke and passive smoking are summarized in table 2 (23, 24, 52–71). In the eight workplace-based studies analyzed by Wells (48), the relative risk of CHD varied between 0.66 and 1.85, and, when the study populations were summarized, the overall risk ratio was 1.18 [95% confidence interval (95% CI) 1.04–1.34]. Of these studies, six were published in international peer review journals and two appeared as doctoral theses. In the three top-rated studies, the combined relative risk was 1.50 (95% CI 1.12–2.01). Partly using the same studies as Wells, Steenland (47) assessed the risk of acute myocardial infarction in association with occupational exposure to environmental tobacco smoke and found a pooled risk ratio of 1.21 (95% CI 1.04–1.41). Most of the studies included in the meta-analyses were small, and the results of single studies were not statistically significant. However, the new studies were consistent with the former ones, and the results of pooled data were statistically significant. Steenland also estimated the absolute risk of CHD in association with exposure to environmental tobacco smoke. The risk of CHD for a nonsmoking worker before the age of 65 years was 4/1000 (95% CI 1/1000–7/1000).

The home environment can expose people to environmental tobacco smoke through spousal smoking. In the meta–analyses by Thun and his colleagues (51), including 17 studies, the risk of CHD for a nonsmoking spouse was increased by 25% (95% CI 1.17–1.33) if the other spouse smoked at home. The result was independent of the gender of the nonsmoking spouse. The relative risks for fatal and nonfatal events were 1.22 (95% CI 1.14–1.30) and 1.32 (95% CI 1.04–1.67). The pooled relative risk was somewhat higher in the case-referent studies, 1.42 (95% CI 1.19–1.81), than in the cohort studies, 1.23 (95% CI 1.15–1.31). In these studies, the number of events in each study was also small, and the results were often nonsignificant. However, when the populations of these 17 studies' were combined, nearly half a million persons were followed up and 7345 CHD events were recorded.

He and his colleagues (50) summarized the results of 17 studies, the same as those analyzed by Thun (51), in a meta-analysis of CHD risk in association with exposure to environmental tobacco smoke both at home and at the workplace. Nonsmokers exposed to environmental tobacco smoke had a relative CHD risk of 1.25 (95% CI 1.17–1.32) when compared with unexposed nonsmokers. The relative risk was 1.21 (95% CI 1.14–1.30) in cohort studies and 1.51 (95% CI 1.26–1.81) in case-referent studies. The relative risks did not differ between the genders. A significant dose-response relation was also identified between the intensity of the exposure and the size of the relative risk.

Table 1. Epidemiologic studies included in six recent meta-analyses on the association between environmental tobacco smoke and cardiovascular disease.

Meta-analysis	Included studies
Law et al, 1997 (46)	Garland et al, 1985 (55), Lee et al, 1986 (58), Svendsen et al, 1987 (60), Hole et al, 1989 (61), Sandler et al, 1989 (62), He, 1989 (57) , Hirayama, 1990 (56) , Humble et al, 1990 (63), Dobson et al, 1991 (64), La Vecchia et al, 1993 (66), He et al, 1994 (67), Tunstall-Pedoe et al, 1995 (69), Layard 1995 (70), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65), Ciruzzi et al, 1998 (53)
Steenland, 1999 (47)	Butler, 1988 (54), He, 1989 (57), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65)
Wells, 1998 (48)	Butler, 1988 (54), Jackson, 1989 (59), Svendsen et al, 1987 (60), Dobson et al, 1991 (64), He et al, 1994 (67), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65)
Kawachi & Colditz, 1999 (49)	Svendsen et al, 1987 (60), Dobson et al, 1991 (64), He et al, 1994 (67), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65)
He et al, 1999 (50)	Garland et al, 1985 (55), Lee et al, 1986 (58), Butler, 1988 (54), Jackson, 1989 (59), Svendsen et al, 1987 (60), Hole et al, 1989 (61), Sandler et al, 1989 (62), He, 1989 (57), Hirayama, 1990 (56), Humble et al, 1990 (63), Dobson et al, 1991 (64), La Vecchia et al, 1993 (66), He et al, 1994 (67), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65), Ciruzzi et al, 1998 (52)
Thun et al, 1999 (51)	Garland et al, 1985 (55), Lee et al, 1986 (58), Butler, 1988 (54), Jackson, 1989 (59), Svendsen et al, 1987 (60), Hole et al, 1989 (61), Sandler et al, 1989 (62), He, 1989 (57), Hirayama, 1990 (56), Humble et al, 1990 (63), Dobson et al, 1991 (64), La Vecchia et al, 1993 (66), He et al, 1994 (67), Steenland et al, 1996 (71), Muscat & Wynder, 1995 (68), Kawachi et al, 1997 (65), Ciruzzi et al, 1998 (52)

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Table 2. Summary of published epidemiologic studies on the association between exposure to environmental tobacco smoke and cardiovascular disease. (95% CI = 95% confidence interval, CHD = coronary heart disease, ECG=elecrocardiography, MI = myocardial infarction)

Publication	Type	Location	Population or participants	Outcome	Exposure	Relative risk	95% CI	Controlled variables
Bonita et al, 1999 (24)	Case-referent	New Zealand	521 cases and 1851 population referents	Stroke	Home and workplace	1.82 2.10 (men) 1.66 (women)	1.34–2.49 1.33–3.32 1.07–2.57	Age, gender, smoking status, and history of hypertension, heart disease or diabetes mellitus
You et al, 1999 (23)	Case-referent	Australia	452 cases (41% smokers) and 452 referents (25% smokers)	Stroke	Cohabitant's smoking	2.03	1.33–3.10	Age, gender, heart disease, hyperten sion, diabetes, education level
Ciruzzi et al, 1998 (52)	Case-referent	Argentina	336 patients and 446 hospital referents	MI	Spouse's and children's smokinig	1.68	1.20–2.37	Age, gender, level of education, body-mass index, hyperlipidemia, history of diabetes or hypertension, family history of CHD
Kawachi et al, 1997 (65)	Cohort	United States	32 046 female nurses	MI and death due to CHD	Home and workplace	1.71	1.03–2.84.	Age, body-mass index, hypertension, hyperlipidemia, diabetes, estrogen replacement therapy, exercise, saturated-at intake, vitamin E intake, alcohol consumption, use of aspirin, parental history of MI
Steenland et al, 1996 (71)	Cohort	United States	479 680 persons	Death due to CHD	Home and workplace	1.22 (men) 1.10 (women)	1.07–1.40 0.96–1.27	Age, gender, level of education, heart disease, body-mass index, hyperten diabetes, aspirin use, diuretic use, sion, estrogen use, alcohol consump - tion, exercise
Muscat & Wynder, 1995 (68)	Case-referent	United States	114 hospital patients and 158 hospital referents	MI	Home and workplace	1.5	0.9–2.6	Age, gender, ethinicity, level of educa-tion, hypertension, calendar year
Tunstall-Pedoe et al, 1995 (69)	Cross-sectional	Scotland	786 nonsmoking men and 1492 nonsmoking women	Symptoms or diagno-sis of CHD, ECG	Self report-ed exposure with cotinine measure-ment	2.7 (highest versus lowest self-reported exposure)	1.3–5.6	Age, gender, housing tenure, serum cholesterol, blood pressure
La Vecchia et al, 1993 (66)	Case-referent	Italy	90 patients and 194 hospital referents	MI	Spousal smoking	1.21	0.57–2.52	Age, gender, level of education, coffee consumption, body-mass index, hypertension, serum cholesterol, diabetes, family history of MI
Dobson et al, 1991 (64)	Case-referent	Australia	343 patients and 825 community referents	MI or death due to CHD	Home and workplace	0.97 (men) 2.46 (women)	0.50–1.86 1.47–4.13	Age, gender, history of heart disease
Humble et al, 1990 (63)	Cohort	United States	513 women over 40 years of age	Death due to CHD	Spousal smoking	1.59	0.99–2.57	Age, serum cholesterol, diastolic blood pressure, body-mass index and square of body-mass index
He, 1989 (57)	Case-referent	China	34 female cases and 64 female referents	MI or ab-normal ECG	Spousal smoking	1.50	0.90–2.51	Age, ethinicity, occupation, are of residence, hypertension, hyperlipidemia, alcohol consumption, exercise, family history of MI
Hirayama, 1990 (56)	Cohort	Japan	91 540 women	Death due to CHD	Spousal smoking	1.31	1.01–1.69	Age
Hole et al, 1989 (61)	Cohort	Scotland	671 men 1784 women	Death due to CHD	Cohabitant's smoking	2.01	1.21–3.35	Age, gender, socioeconomic status, diastolic blood pressure, serum choles-terol, body-mass index
Sandler et al, 1989 (62)	Cohort	United States	4162 men 14 873 women	Death due to CHD	Home	1.31 (men) 1.19 (women)	1.05–1.64 1.04–1.36	Age, gender, marital status, level of education, quality of housing
Svendsen et al, 1987 (60)	Cohort	United States	1245 men	MI or death due to CHD	Spousal smoking	2.11	0.69–6.46	Age, blood pressure, serum cholesterol, body weight, alcohol consumption, level of education
Lee et al, 1986 (58)	Case-referent	United Kingdom	118 patient and 451 hospital referents	CHD	Spousal smoking	0.9	0.5–1.6	Age, gender, hospital region
Garland et al, 1985 (55)	Cohort	California	695 women, ages 50–79 years	Death due to CHD	Spousal smoking	2.7	0.9–13.6	Age, systolic blood pressure, serum cholesterol, body-mass index, years of marriage
He et al, 1994 (67)	Case-referent	China	59 cases and 126 referents	Nonfatal CHD event	Home and workplace	1.95 (work) 2.36 (work and home)	0.90–4.10 1.01–5.55	Age, history of hypertension, type A personality, total and high-density lipoprotein cholesterol levels

Howard & Thun (72) estimated the risk of CHD in association with exposure to environmental tobacco smoke indirectly based on the data of nine studies on CVD risk among active smokers. They used a linear regression model to calculate the risk for smoking 0.55 cigarettes per day, which they chose to represent the

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dose of environmental tobacco smoke per day for nonsmokers. The estimated risk ratio varied between 1.13 and 1.47, and the pooled risk was 1.32.

Risk of stroke in association with exposure to environmental tobacco smoke

Most of the epidemiologic studies on the cardiovascular effects of environmental tobacco smoke cover only CHD. Studies on the effects of environmental tobacco smoke on cerebral arteries or peripheral circulation are scant. As far as we know, there are only two studies on the association of exposure to environmental tobacco smoke with cerebrovascular disease (23, 24) (table 2). In the case-referent study of Bonita et al (24), 521 stroke patients were compared with 1851 age- and gender-matched population referents. The men exposed to environmental tobacco smoke had a 2.1 times higher risk (95% CI 1.33–3.32) for stroke than the unexposed men. For the women the odds ratio was 1.66 (95% CI 1.07–2.57). In comparison, respective odds ratios for active smoking, as compared with nonsmoking, were 4.07 (95% CI 2.74–6.04) for the men and 4.50 (95% CI 3.03–6.69) for the women.

Subclinical effects of environmental tobacco smoke on the cardiovascular system

Asymptomatic subclinical vascular disease predicts additional vascular symptoms and events. Most studies on the association between exposure to environmental tobacco smoke and acute CVD events suffer from a relatively small number of end-point events. Therefore, measures of subclinical disease offer increased statistical power, either by providing a continuous outcome measure, instead of a dichotomous one, or by increasing the number of events by including also clinically silent disease events.

Both active and passive smoking are associated with arterial wall IMT (73). According to the results of the Atherosclerosis Risk in Communities study, a nonsmoker exposed to environmental tobacco smoke had a thicker carotid artery intima-media at the beginning of the study, as compared with unexposed nonsmokers (74). Moreover, IMT increased significantly more among people exposed to environmental tobacco smoke than among unexposed subjects during the follow-up of the study cohort. It has been shown that even relatively small differences in IMT are significant predictors of future acute cardio- and cerebrovascular events (74–76).

Endothelial dysfunction is considered to be a marker of early vascular damage (77). Among humans, endothelial function can be assessed by measuring vascular reactivity in the brachial artery with ultrasound. Although only superficial systemic arteries can be measured, endothelial dysfunction of the brachial artery correlates with both coronary endothelial dysfunction and coronary atherosclerosis (78). Exposure to environmental tobacco smoke seems to impair endothelial function both in Caucasian and Asian populations (78–81).

Exposure to environmental tobacco smoke also affects the hemostatic system. Plasma fibrinogen levels are known to correlate with CHD risk (35, 36, 82, 83). Among nonsmoking Japanese women, exposure to environmental tobacco smoke increased plasma fibrinogen levels markedly (37). The effect of environmental tobacco smoke on plasma fibrinogen levels was about 40–60% of that of current active smoking.

Noninvasive magnetic resonance imaging has allowed the assessment of silent cerebral infarctions also in population-based epidemiologic studies. The association of current smoking, previous smoking, and exposure to environmental tobacco smoke with the presence of silent cerebral infarctions in the general population was evaluated in the Atherosclerosis Risk in Communities study (84). The relative risk for the occurrence of silent cerebral infarctions was 1.88 (95% CI 1.13–3.13) for active smokers, 1.16 (95% CI 0.74–1.83) for ex-smokers, and 1.06 (95% CI 0.64–1.75) for nonsmokers exposed to environmental tobacco smoke as compared with unexposed nonsmokers.

Experimental evidence

In experimental studies human subjects or laboratory animals are exposed to small amounts of sidestream tobacco smoke. Experimental studies are an important complement to epidemiologic studies because they are free from misclassification, the dose of the exposure can be exactly defined, and the potential effect of confounding factors can be minimized. The experiments are also informative regarding the biological and pathogenetic effects of tobacco smoke. However, the duration of an experimental study is always limited when compared with the years, or decades, of long exposure in real life.

Blood clotting and thrombus formation usually precede an acute CHD event (85). In healthy nonsmoking human volunteers, exposure to environmental tobacco smoke for 15–60 minutes significantly increased platelet adhesion and blood coagulability (72, 86, 87). Already 20 minutes of exposure to environmental tobacco smoke is enough to increase platelet adhesiveness nearly to the same level as active smoking (87). The phenomenon can be observed at the exposure levels common in many bars and restaurants where smoking is not restricted. Among nonsmoking persons, the hypercoagulable state that has been demonstrated after

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exposure to environmental tobacco smoke is equivalent to changes in smokers who consume one to two cigarettes after abstinence (85, 88, 89). The duration of the effect of tobacco smoke to platelet activity is short, having a half-time of approximately 1 hour.

Injury of the arterial endothelial layer is another mechanism by which tobacco smoke can contribute to the development of atherosclerotic disease (77). Already relatively low levels of the environmental tobacco smoke have been shown to cause endothelial damage and arterial plague formation in animal models (90–92). The endothelial damage may partly be mediated through the lipid oxidation reactions caused by tobacco smoke (93). The effect of environmental tobacco smoke on cardiac exercise tolerance has been assessed in experimental studies. A significant reduction in exercise tolerance has been observed both for healthy females and, particularly, for male CHD patients (94–96).

Possible biases in epidemiologic studies

The following potential sources of bias need to be considered in the evaluation of epidemiologic studies: publication bias, selection, confounding, and misclassification. Publication bias results from the probability of publication being higher if the results of the study are significant. Negative findings may not have been submitted to a journal, or the manuscripts have not been accepted for publication. Meta-analyses also use various inclusion criteria, and these criteria may favor certain types of studies. However, in the past 15 years, over 20 epidemiologic studies have been published on the association between exposure to environmental tobacco smoke and the risk of CVD. Therefore, even though some negative studies may have gone unpublished, the inclusion of their results would probably not have markedly changed the results of the meta-analyses and the general picture of the role of environmental tobacco smoke in CVD risk. It is also important to remember that one reason for not observing an association between the exposure and the outcome is the insufficient quality of measurements.

The common element in selection is that the relation between the exposure and the disease differs for those who participate and those who would be theoretically eligible for study but did not participate. Selection is a potential problem mainly in case-referent studies. An overrepresentation of subjects exposed to environmental tobacco smoke among cases or underrepresentation among referents biases the results towards a false positive association, and the vice versa situation can bias the results towards the false negative. In cohort studies selection can cause a false positive association if the case finding during the follow-up is incomplete, and the subjects exposed to environmental tobacco smoke are overrepresented among the cases found. Even though some selection cannot be avoided, it is not plausible that a systematic selection could explain the association found between exposure to environmental tobacco smoke and CVD in many studies.

Many factors have been shown to be statistically associated with the risk of CVD. However, the number of factors with a biologically plausible causal relation is much smaller. Besides smoking, other well-established CVD risk factors include high serum total cholesterol, low HDL cholesterol, high blood pressure, diabetes, lack of physical activity, overweight, and heredity (12, 97–101). It is possible that the subjects exposed to environmental tobacco smoke differ from the unexposed subjects with regard to these risk factors and that the observed difference between the groups in CVD risk depends on these confounding factors rather than on exposure to environmental tobacco smoke.

Controlling of confounding requires data on the occurrence of possible confounding factors in the study population. The comprehensiveness of these data and the measurement precision of these factors vary in different studies. It has been shown, however, that including even a large number of possible confounding factors in the analyses usually explains only a relatively small portion of the observed association between environmental tobacco smoke and CVD risk. The Nurses' Health Study in the United States reported the CHD risk of exposed persons to be 1.97 times higher than that of unexposed persons. After control for 14 possible confounding factors, the risk was still 1.74 times higher (65). A limitation of the Nurses' Health Study was that it did not include measurements of biological risk factors, such as blood pressure and serum lipids.

Socioeconomic status is a putative confounding factor, which can bias the association between exposure to environmental tobacco smoke and CVD risk (71). Steenland (71) conducted separate analyses for blue-collar and white-collar workers and found that environmental tobacco smoke in the workplace was related to CHD risk only among male blue-collar workers. On the other hand, in the Nurses' Health Study, in which the study cohort was relatively homogeneous and several factors related to socioeconomic status were controlled, the confounding factors explained only a quarter of the overall risk associated with environmental tobacco smoke (65). Confounding can also act in the other direction and diminish the observed association between environmental tobacco smoke and CVD risk. It can be assumed, for example, that exposure to environmental tobacco smoke is associated with alcohol consumption, which may have a protective effect against CVD (102).

In epidemiologic studies the study population needs to be correctly classified according to the exposure.

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Nondifferential misclassification always causes a bias towards the null, but a differential misclassification can cause bias to either direction. A situation in which a differential misclassification may cause a biased positive association between environmental tobacco smoke and CVD risk arises if smokers exposed to environmental tobacco smoke are classified as nonsmokers. Even though some smokers may deny their smoking in epidemiologic studies, the phenomenon is fairly rare. The reliability of self-reporting can be assessed by using objective methods. In the CARDIA (Coronary Artery Risk Development in Yong Adults) study, for example, only 1.3% of the people who reported that they were nonsmokers were, according to cotinine measurements, probably active smokers (103).

On the other hand, a nondifferential misclassification of study subjects according to their exposure to environmental tobacco smoke is likely to be more common than differential misclassification. If an exposed person is classified as unexposed, or vice versa, the probability of observing the existing association between the exposure and CVD can substantially diminish. Similarly, difficulties to define the quantity and duration of the exposure usually reduce the possibilities to observe an association between the exposure and disease.

Is there a discrepancy in the estimated risk of cardiovascular disease in association with environmental tobacco smoke as compared with active smoking?

Generally it can be stated that the CVD risk associated with environmental tobacco smoke is larger than expected. The amount of nicotine absorbed by a nonsmoker from the air is 1% of the amount of nicotine inhaled from 20 cigarettes, which is a fairly common number of cigarettes smoked per day (104). Exposure to environmental tobacco smoke increases CHD risk, however, by 25–35%. Thus the overall risk is about one-third the risk observed in many studies among active smokers.

However, several factors can explain the relatively small difference in CVD risk between active and passive smokers. First, it is possible, that active smoking itself is a stronger risk factor for CVD than previously reported (18). Second, experimental studies have shown that already very low tobacco smoke concentrations affect the circulatory system through several pathways, and the dose-response relation may be nonlinear (37, 74, 78–81, 85–89, 105, 106).

In most prospective cohort studies data on smoking have been collected only once at the beginning of the study, and the changes in smoking behavior have not been verified during the follow-up period. Most prospective follow-up studies have been carried out in countries of western Europe, the United States, Canada, and Australia, where the prevalence of smoking, particularly among middle-aged and older men, is rapidly decreasing. In Finland, for example, nearly half of adult male smokers quit smoking during a period of up to 20 years (107). Cumulative misclassification of smoking status during the follow-up weakens observed associations between smoking and CVD. We have shown before that the risk ratio of CHD death in association with smoking at the beginning of a study decreases markedly, from 6.99 (95% CI 1.61–30.4) to 2.07 (95% CI 1.68–2.55) when the period of follow-up is extended from 2 to 20 years (18). Furthermore, in most epidemiologic studies, passive smoking among a nonsmoking group has not been taken into account in the analyses, and, therefore, the risk of CHD among smokers, as compared with nonsmokers, has been underestimated (105, 108, 109).

The relatively high CHD risk associated with exposure to environmental tobacco smoke is also supported by the findings of experimental studies. Particularly the effect of environmental tobacco smoke on the hemostatic system and platelet activity can explain why exposure to environmental tobacco smoke increases the risk of CHD more than what can be estimated directly on the basis of the intensity of tobacco smoke exposure (72, 85, 88, 110, 111). Law et al (46) estimated, on the basis of results of experimental studies, that the increase in platelet adhesion capacity caused by environmental tobacco smoke can increase the risk of CHD among nonsmoking persons by 20–30%.

To quantify the excess risk of an acute CHD event due to environmental tobacco smoke, we estimated the population attributable risk using data from Finland as an example. According to data from an adult health behavior survey, approximately 14% of nonsmoking adult males and 13% of nonsmoking adult females are exposed to the environmental tobacco smoke at least 1 hour daily either at their workplaces or in their homes (112). On the assumption that the relative risk of an acute CHD event is 1.25 when nonsmokers exposed to environmental tobacco smoke are compared with unexposed nonsmokers, it can be estimated that the population attributable risk is 3.4% for men and 3.1% for women. If we assume that the relative risk is 1.35, the population attributable risk increases to 4.7% for men and 4.4% for women. Since there are approximately 12 500 CHD events per year among men in Finland, at least in principle, between 400 and 600 CHD events could be avoided annually among men if exposure to environmental tobacco smoke could be eliminated. Among women, around 10 500 CHD events occur annually in

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Finland. Of these, between 300 and 450 annual events could be due to environmental tobacco smoke. However, these are rough estimates, which should be interpreted with caution, because of obvious limitations with the quantification of the exposure and other assumptions inherent in these calculations.

Concluding remarks

Since the 1950s, hundreds of studies have confirmed the association of smoking with CVD risk. Most studies report a 1.5- to 2.5-fold increase in the risk of CHD and stroke for smokers in comparison with nonsmokers. This increased risk can be observed also for persons who smoke infrequently or occasionally, and no limit for safe smoking can be determined.

According to the results of epidemiologic and experimental studies, also environmental tobacco smoke has marked harmful effects on the cardiovascular system. The strongest evidence is available for the role of environmental tobacco smoke in CHD risk. It can be estimated, on the basis of different study designs and methods, that exposure to environmental tobacco smoke increases the risk of an acute CHD event by 25–35%. This estimate would suggest that, in a country like Finland, with five million inhabitants, around 700–1000 CHD events occur annually due to exposure to environmental tobacco smoke.

The data on the role of environmental tobacco smoke in the risk of stroke are scarce, but the relative risk is probably at least as high as for CHD. The results from experimental studies support the findings of epidemiologic studies and provide several biologically plausible mechanisms to explain the relatively high CVD risk associated with exposure to environmental tobacco smoke. Even though the number of studies conducted in the work environment is still small, there is no reason to assume that the cardiovascular effects of environmental tobacco smoke would markedly differ between the home and the workplace.

It can be criticized that most of the studies on the association between environmental tobacco smoke and CVD risk are small, and the results of single studies have rarely been statistically significant. However, the results of different studies have been consistent, and the results of analyses based on pooled data from different studies have been highly significant. It is not likely that publication bias, selection, confounding, or misclassification can explain the association between environmental tobacco smoke and CVD risk.

Thus environmental tobacco smoke is harmful to cardiovascular health and an important public health problem in many populations. Firm and timely actions are needed to protect people from exposure to environmental tobacco smoke, in both occupational and other environments.

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